

ACTOS FAMILY®-- MONTANA CLINICAL UPDATE

The ACTOS family of products provides 3 options for the treatment of type 2 diabetes mellitus (T2DM): ACTOS (pioglitazone hydrochloride), ACTO*plus* met™ (pioglitazone hydrochloride and metformin hydrochloride), and DUETACT™ (pioglitazone hydrochloride and glimepiride). Information regarding the indication and mechanism of action for each product is provided in the table below.

Indication and Mechanism of Action for ACTOS Family Products.(1, 2,3)

Product	Indication	Mechanism of Action
ACTOS	Once daily monotherapy and in combination with a sulfonylurea, metformin, or insulin when diet and exercise plus the single agent do not result in adequate glycemic control.	Decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output.
ACTO<i>plus</i> met	An adjunct to diet and exercise to improve glycemic control in patients with T2DM who are already treated with a combination of ACTOS and metformin or whose diabetes is not adequately controlled with metformin alone, or for those patients who have initially responded to ACTOS alone and require additional glycemic control.	Thiazolidinediones (ACTOS)--see above. Biguanides (metformin) act primarily by decreasing endogenous hepatic glucose production.
DUETACT	An adjunct to diet and exercise as a once-daily combination therapy to improve glycemic control in patients with T2DM who are already treated with a combination of ACTOS and SU or whose diabetes is not adequately controlled with a SU alone, or for those patients who have initially responded to ACTOS alone and require additional glycemic control.	Thiazolidinediones (ACTOS)--see above. Sulfonylureas (glimepiride), an insulin secretagogue, act primarily by stimulating insulin release from functioning pancreatic beta cells.

SU=sulfonylurea.

Clinical Update

The following summarizes the clinical information released since the previous submission of the ACTOS clinical update. Formulary dossiers containing complete product information for ACTOS, ACTO*plus* met, and DUETACT are available upon request. Please refer to the enclosed package inserts for complete safety information.

PROactive

Safety data from the PROactive study has been incorporated in the adverse events and warnings sections of the ACTOS 2007 prescribing information.

PROactive (**PRO**spective **Pi**oglit**A**zone **C**linical **T**rial In **MacroV**ascular **E**vents) was a randomized, double blind, placebo-controlled outcome study designed to determine the effects of ACTOS (added to standard of care treatment) on mortality and morbidity associated with cardiovascular disease progression in more than 5,000 high-risk patients with T2DM. (4,5) In PROactive, patients with T2DM and a history of macrovascular disease received either conventional oral therapy for T2DM or had their therapy supplemented with ACTOS (forced titration from 15 to 30 to 45 mg, dependent upon tolerability). Blinded follow-up continued until both of the following criteria were fulfilled: a) the last patient recruited was observed for at least 30 months; and b) the number of patients with one or more end point events was at least 760.

- The primary composite endpoint (all cause mortality, nonfatal myocardial infarction (MI) (including silent MI), stroke, acute coronary syndrome, surgical intervention on coronary or leg arteries, or amputation above the ankle) was reduced by 10% (hazard ratio [HR]=0.9), but had not reached statistical significance by study end ($P=0.095$). (4,5)

- The main secondary endpoint of life-threatening events, showed that ACTOS significantly reduced the combined risk of heart attacks, strokes, and death by 16% (HR 0.84; $P=0.027$).^(4,5)
- Overall safety and tolerability was consistent with the known adverse event profile of ACTOS.⁽⁵⁾ Compared with placebo, more patients in the ACTOS group were hospitalized with heart failure, 4% (108/2633) and 6% (149/2065), respectively. However, heart failure mortality rates did not differ between treatment groups.⁽⁵⁾

The authors concluded that ACTOS improves cardiovascular outcomes in patients with type 2 diabetes and macrovascular disease.⁽⁵⁾

PROactive Subgroup Analysis - Patients With or Without Previous Stroke

From the PROactive study, patients with or without a history of stroke (≥ 6 months before randomization) were included in a prespecified subgroup analysis.⁽⁶⁾ Specifically, the analysis evaluated 1) time to fatal or nonfatal stroke and 2) time to cardiovascular death, nonfatal MI (excluding silent MI), or nonfatal stroke. Stroke was determined by the following criteria: an acute, focal neurological deficit lasting longer than 24 hours or resulting in death within 24 hours of the onset of symptoms attributable to a cerebral vascular lesion. Occurrences of subarachnoid hemorrhage were excluded. Cases of fatal stroke were determined by adjudication.

Results

Baseline characteristics differed between patients with and without a history of previous stroke.⁽⁶⁾ For patients with previous stroke, there was a higher rate of hypertension and microvascular disease, and higher mean blood pressure (145/84 mmHg vs 143/83 mmHg, respectively). There were more males, a higher rate of previous macrovascular disease, and greater use of lipid-altering therapy for patients without previous stroke.

The prespecified subgroup analysis of patients with previous stroke demonstrated a significant risk reduction of 47% of a recurrent stroke (fatal/nonfatal) with ACTOS compared to placebo (HR 0.53; $P=0.0085$; Table 1 and Figure 1).⁽⁶⁾ In addition, the combined risk of cardiovascular death, nonfatal stroke, or nonfatal MI (excluding silent MI) was also significantly reduced in the ACTOS group compared to placebo for patients with previous stroke (HR 0.72; $P=0.0467$). Treatment with ACTOS had no significant effect on any of the endpoints for patients without a previous stroke.

Effect of ACTOS or Placebo Add-on on Cardiovascular Events.⁽⁶⁾

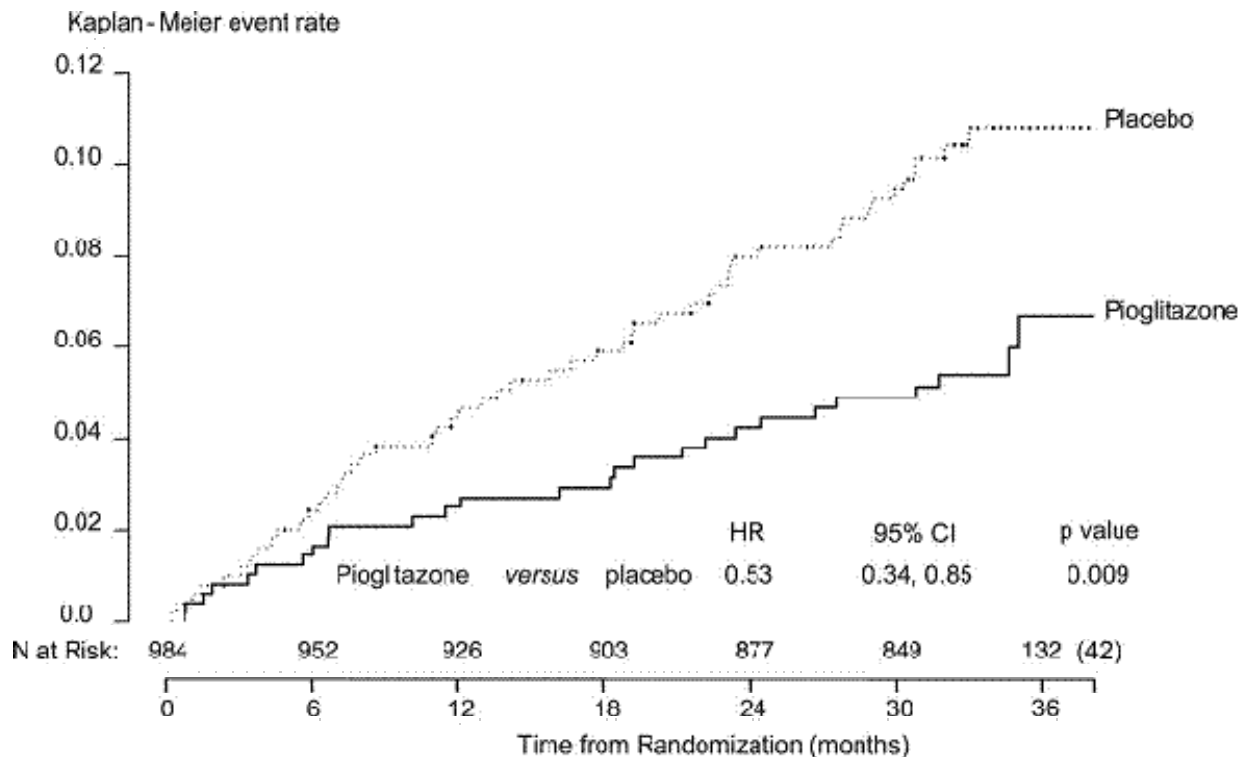
Endpoints	Previous Stroke			No Previous Stroke		
	ACTOS n=486	Placebo n=498	HR* P Value	ACTOS n=2119	Placebo n=2135	HR* P Value
Total Stroke	27 (5.6%)	51 (10.2%)	0.53 =0.0085	59 (2.8%)	56 (2.6%)	1.06 =0.767
Cardiovascular death, nonfatal stroke, or nonfatal MI†	63 (13.0%)	88 (17.7%)	0.72 =0.047	194 (9.2%)	225 (10.5%)	0.86 =0.129

HR=hazard ratio; MI=myocardial infarction.

*ACTOS vs placebo.

†Excluding silent MI.

Time to Stroke (Fatal and Nonfatal) in Patients With Previous Stroke.(6)



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Multivariate analyses of baseline characteristics for patients with previous stroke revealed that the use of ACTOS ($P=0.0076$) and statins ($P=0.0126$) were the only significant factors that effected the risk of recurrent stroke with an associated risk reduction of approximately 50% each.(6) For patients without previous stroke, significant factors for a first stroke were age, A1C, creatinine ≥ 130 $\mu\text{mol/L}$, and peripheral arterial disease. Prior stroke was the strongest predictor of recurrent stroke for the entire cohort (HR 2.88; $P<0.0001$).

Safety

For patients with previous stroke, no differences in serious adverse events were noted (49% for ACTOS vs 51% for placebo).(6) Heart failure requiring hospitalization was 6.4% versus 4.0% ($P=0.0946$) and 1.2% versus 0.8% ($P=0.50$) for fatal heart failure in the ACTOS and placebo groups, respectively.

Serious adverse events for patients without previous stroke were 46% for ACTOS vs 48% for placebo.(6) Heart failure requiring hospitalization was significantly more in the ACTOS group (5.6%) compared to the placebo group (4.1%; $P=0.0279$). However, fatal heart failure was not different between groups (0.9% ACTOS vs 0.8% placebo; $P=0.8508$).

Conclusion

Based on this subgroup analysis of the PROactive study, the authors concluded that ACTOS reduced the risk of recurrent stroke significantly in high-risk patients with T2DM.(6)

ACTOS and Recurrent MI

A subgroup analysis of the PROactive study investigated the effect of ACTOS on recurrent MI in subjects with a history of MI stratified by age, gender, and duration of T2DM.(7) Six hundred forty-one female and 1,804 male patients with a previous history of MI (≥ 6 months prior to randomization) were included in the analysis. Recurrence of MI (fatal or non-fatal, excluding silent MI) was significantly lower in the ACTOS group compared with the placebo group (5.3% vs 7.2% respectively; HR=0.72, $P=0.045$). Gender ($P=0.53$), age (<65 years/ ≥ 65 years; $P=0.43$), or T2DM duration (<5 years/5-10 years/ ≥ 10 years; $P=0.46$) had no significant effect on the HR for time to recurrent MI. The authors concluded that the effect of ACTOS on recurrent fatal or non-fatal MI was better than placebo regardless of gender, age, or duration of T2DM.

CHICAGO

The effect of ACTOS on measures of atherosclerotic disease progression was evaluated in a 72-week study (Carotid intima-media thickness in Atherosclerosis using pioGlitazOne).(8) The trial was a prospective, multicenter, randomized, double-blind study that randomized 462 ethnically/racially diverse patients with newly diagnosed T2DM from a large metropolitan area. Patients were randomized to receive ACTOS (up to 45 mg/d) or glimepiride (1-4 mg/d) in addition to their current antidiabetic regimen (monotherapy or combination therapy of sulfonylurea/metformin, or any of those plus insulin).

- The mean change from baseline in CIMT was significantly reduced for ACTOS compared to glimepiride (difference in absolute change from baseline was -0.013 mm [$P=0.02$]).(8) Over the course of the study period, the mean change from baseline in posterior wall mean CIMT for ACTOS diverged from glimepiride starting at week 24 and remained progressively diverged at week 48 and at final visit.
- The dropout rate was approximately 30% but similar in both groups. In the ACTOS group, 1 case of congestive heart failure was reported.(8) Peripheral edema and weight gain were more common in the ACTOS group and hypoglycemia was more common in the glimepiride group. Mean weight gain was 3.2 kg for ACTOS and 1.0 kg for glimepiride by final visit.

According to the authors, ACTOS slowed the progression of CIMT compared to glimepiride in a racially and ethnically diverse cohort of patients with better cardiovascular risk factor management (high statin use, LDL-C near 100 mg/dL, and well-controlled blood pressure).(8) The authors stated that additional data will be necessary to evaluate the routine use of ACTOS instead of glimepiride to substantially reduce major cardiovascular events.

PIPOD

The Pioglitazone in Prevention Of Diabetes (PIPOD) open-label, 3-year study was conducted to evaluate beta-cell function, insulin resistance, and the incidence of diabetes during treatment with ACTOS in Hispanic women with prior gestational diabetes who had completed participation in the TRIPOD study.(9) Patients were initiated with ACTOS 30 mg/d which was titrated to 45 mg/d for the remainder of the study.

Of the 95 patients who were deemed not to have diabetes at the end of TRIPOD, 89 patients participated in the PIPOD study and 86 completed at least 1 follow-up visit.(9) Overall, 11 patients had diabetes at 1 or more oral glucose tolerance tests during a median of 35.9 months of ACTOS therapy. The average annual incidence rates of diabetes were 5.2% during ACTOS treatment and 4.6% during the entire observation period, including the post-drug washout period. The final cumulative incidence of diabetes during treatment and post-drug follow-up was 17%. These rates were similar to rates observed during a median of 31 ± 8 months of

troglitazone treatment and post-trial washout in the TRIPOD study (5.7% and 25% per year, respectively) and lower than rates observed during a median of 28±8 months of placebo treatment and post-trial washout in the TRIPOD study (13.1% and 52% per year, respectively).

Two significant and independent predictors of developing diabetes were the change in IVGTT total insulin area during the first year of treatment ($P=0.001$) and baseline OGTT glucose area ($P=0.02$).⁽⁹⁾ Incidence of diabetes was lowest in women with the greatest reduction in insulin output and highest in women with the smallest reduction after 1 year of treatment.

Comparison of changes in beta-cell compensation for insulin resistance across the TRIPOD and PIPOD studies revealed that ACTOS stopped the decline in beta-cell function that occurred during placebo treatment in the TRIPOD study and maintained the stability of beta-cell function that occurred during treatment with troglitazone.⁽⁹⁾ The authors concluded that TZDs may alter the progression to T2DM in high risk Hispanic patients and additional studies are required to assess the benefits in other high risk groups.

References

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- 8 Mazzone T, Meyer PM, Feinstein SB, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes. *JAMA*. 2006;296:2572-2581.
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